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| EXAMINER | |
|---|---|
| MCCORMICK, MELENIE LEE | |

| ART UNIT | PAPER NUMBER |
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| 1655 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/538,223 | SCHNEIDER, HEINZ | |
| | Examiner | Art Unit | |
| | MELENIE MCCORMICK | 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3-7,9,10,16,18,21 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7,9,10,16,18,21 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's remarks with claim amendments submitted 24 November 2008 have been received and considered.

Claims 3-7, 9, 10,16,18,21 and 25-33 are pending and presented for examination on the merits.

### *Withdrawn Rejections*

The previous rejection under 35 U.S.C. 102(b) has been withdrawn in light of the claim amendment which adds the limitation 0.1-150 grams/100 ml of said formulation.

The previous rejection under 35 U.S.C. 103(a) has been withdrawn in light of the amendment to the claims, which now require particular amounts of the NO donor, including glutamine and the addition of new claims drawn to glutamine as a di or tri-peptide.

### *New Rejections*

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 and 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaynor et al. (US 5,904,924).

Gaynor et al. teaches a nutritional powder formulation comprising 250 mg glutamine and Japanese green tea standardized to 7.5% catechins predominantly as EGCG (i.e. a green tea extract). Gaynor et al. further teaches that the composition may be added to 10 to 20 ounces of water (see e.g. col 4, lines 15-66). In 10 ounces of water, 250 mg of glutamine is .845 g / 1000 ml and .422 g /1000 ml in 20 ounces of water. These amounts are squarely within the amount instantly claimed.

Therefore, the reference is deemed to anticipate the instant claims above.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 18-19, and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaynor et al. (US 5,904,924) in view of Itou et al. (JP 409012454).

Gaynor et al. teaches a nutritional powder containing glutamine in the amount claimed and green tea extract containing EGCG and is relied upon for the reasons set forth above.

Gaynor et al. does not explicitly teach that the composition comprises theanine.

Itou et al. teach that theanine is one of the amino acids in green tea which is present in large amounts and responsible for the delicious flavor.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to include theanine in the composition taught by Gaynor since theanine is part of green tea (a component of Gaynor's composition) and because it enhances the flavor of green tea. Therefore, because Gaynor teaches a beverage, a person of ordinary skill in the art would have been motivated to include this component of green tea in order to enhance the flavor of the beverage taught by Gaynor.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-7, 9-10, 16, 18-19, 21, and 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhong et al. (2002), Schnieider et al. (US 6,656,608), Sherrat et al. (US 6,423,349), Furst et al. (1990), Schnieder et al. (5,902,829), and Yokozowa et al. (2002).

Zhong et al. beneficially teach that Green tea (*Camellia sinensis*) contains high levels of polyphenols including (+) catechin, (-) epicatechin, (+) gallocatechin, (-) epigallocatechin, (-) epicatechin gallate and (-) gallocatechin gallate (see e.g. G957 and Table 1 on page G958). Zhong et al. further teach that green tea extract scavenges free radicals in the liver and after ischemia-reoxygenation (see e.g. abstract). Zhong et al. further teaches that rats were given green tea extract for five days prior to surgery and that hepatic ischemia was induced and then the ischemic liver was repurfused see e.g. pages G957-G958 -Methods).

Schneider et al. '608 beneficially teach that glycine is useful in protecting against damage caused by ischemia reperfusion. Schneider et al. further beneficially teach that a composition comprising glycine is intended to be administered orally (see e.g. col 5 line 66-col 6 line 2). Schneider et al. also further beneficially teach that the composition is intended as a pre-operative treatment (see e.g. col. 6 lines 21-23).

Sherratt et al. beneficially teach that glutamine can be used for promoting recovery in patients undergoing elective surgery and for treating multiple organ system failure (see e.g. col 1, lines 7-10). Sherratt et al. further teach that multiple organ system failure is associated with ischemia reperfusion injury and that oxygen radicals are

involved during ischemia followed by reperfusion (see e.g. col 2, lines 38-40). Sherratt also teaches that therapy to prevent the generation of free radicals and to promote the generation of radical scavengers when radicals have been generated are essential to the treatment of multiple organ system failure and that the body's natural antioxidant defenses against free radicals consist primarily of glutathione peroxidase, catalase and superoxide dismutase (see e.g. col 2, lines 40-47 and lines 59-61). Sherratt also discloses that glutamine has been implicated as sustaining mucosal architecture and function by scavenging free radical and preventing lipid peroxidation. Sheratt also teaches that in addition, glutamine combines with N-acetyl cysteine to form glutathione and, in a reaction catalyzed by the selenium-containing enzyme, glutathione peroxidase, glutathione is transformed to oxidized glutathione. Sherratt et al. further teach that this then combines with hydrogen peroxide and degrades it to water, preventing hydrogen peroxide from reacting with superoxide to produce a hydroxyl radical (see e.g. col 5, lines 22-30). Sherratt et al. further teach a method of promoting recovery from an elective surgical procedure comprising administering to a patient in need thereof, prior to said elective procedure, a composition comprising L-glutamine (see e.g. col 4, lines 8-15). Sherratt et al. further teach that glutamine is a free radical scavenger and that glutamine is administered to patients in order to promote the recovery of elective surgery (see e.g. col 5, lines 22-37 and lines 45-63 and claim 1). Sherratt et al. further teach that the composition is administered to patients prior to elective surgery, particularly for two days prior to the surgery (see e.g. claim 9) and that the administration is oral or via a feeding tube (see e.g. col 10, lines 8-10).

Furst et al. beneficially teaches that a di-peptide form of glutamine is useful for parenteral administration due its higher stability as compared to free glutamine (see e.g. abstract).

Schneider et al. '829 beneficially teach a composition and a method of administering the composition pre-operatively which reduces the risk of reperfusion injury in patients who undergo elective surgery (see e.g. col 1, lines 21-26). Schneider et al. further teach that L-arginine or a precursor of L-arginine is used for this purpose (see e.g. col 1, lines 27-34). It is further disclosed by Schneider et al. a precursor of L-arginine which may be used pre-operatively is glutamine (see e.g. col 1, lines 35-36 and claim 4).

Yokozowa et al. beneficially teach that theanine is one of the major components of green tea and that it was able to inhibit lipid peroxidation (see e.g. abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Zhong et al. and the glycine and glutamine taught by Schneider et al. '608 and Sherratt et al. and Schneider '829, respectively, to obtain a composition which would be useful for treating preoperative patients to reduce the risk of ischemia reperfusion. Since it is well known in the art that the majority of damage resulting from ischemia reperfusion is related to oxidative stress, it would have been obvious to the skilled artisan and the skilled artisan would have been motivated and would have had a reasonable expectation of success in combining a well known antioxidant (green tea extract) with glutamine, especially since,

as disclosed by Sherratt and Schneider et al. '829, glutamine is useful in protecting against of post operative reperfusion injury. Since glutamine has a known therapeutic effect (reducing the effects of ischemia reperfusion), a person of ordinary skill in the art would have a reasonable expectation of success in optimizing the amount of glutamine used in order to achieve a desirable therapeutic effect. Since it has also been shown that glycine may be useful as a treatment to protect against ischemia reperfusion (as disclosed by Schneider et al. '608), it would have been obvious to include this compound in composition which was to be used for the same purpose. It would have further been obvious to use a green tea extract, such as that taught by Zhong, which contains theanine. A person of ordinary skill in the art would have been motivated to do so based upon the beneficial teaching of Yokazawa et al. that theanine, like polyphenols from green tea, are a major component in green tea extracts and have antioxidant activity. Therefore, a person of ordinary skill in the art would have recognized the benefit in providing a green tea extract which contains theanine since Sheratt et al. teach that ischemia reperfusion can be reduced by administering radical scavengers (antioxidants) prior to an ischemic event, such as surgery. In addition, a person of ordinary skill in the art would have a reasonable expectation of success in using a di-peptide containing glutamine as the glutamine source rendered obvious by the above cited references because Furst et al. teaches the improved stability of this form and its use for parenteral administration. Please note that the administration times taught by the instantly cited references would render obvious the instantly claimed administration which takes place less than twenty four hours prior to surgery because the references teach administration

which *begins* before the surgery. Administration that begins any time prior to surgery and continues until the surgery would be taking place less than twenty four hours prior to surgery, as instantly claimed. Moreover, Zhong teaches that rats are fasted overnight before surgery. Therefore, they are provided with green tea up until at least 12 to 8 hours before surgery (which is what a person of ordinary skill in the art would interpret 'overnight' to mean) . The adjustment of particular conventional working conditions (e.g. administering the composition to a patient at a particular hour before or after surgery) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

***Response to Arguments***

Although the previous rejection under 35 U.S.C. 103(a) has been withdrawn, arguments pertinent to the current rejection are addressed below.

Applicants have summarized the prior rejection.

Applicants argue that none of the cited references, alone or in combination, disclose or suggest the claimed methods of averting or reducing the risk of postoperative complications wherein a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tri-peptide containing glutamine, or the physiologically tolerated salts or combinations thereof, is gastrointestinally administered to a surgical patient, wherein administration of the

composition takes place less than twenty four hours before a surgical procedure. This is not found persuasive and the motivation to administer such a composition is discussed above. Applicants also argue that there is no disclosure or suggestion in the references of administration of a composition comprising a) green tea extract and b) at least one precursor of glutamine in the form of a di or tri peptide containing glutamine or the physiologically tolerated salts thereof, or combinations thereof, for averting or reducing the risk of postoperative complications, as claimed in new claim 33 or the formulation of new claim 27. This is also not found persuasive and the new limitation wherein the glutamine is a dipeptide is rendered obvious by the teachings of Furst et al. that a dipeptide form of glutamine is more stable than free glutamine. Applicants also argue that there is no disclosure or suggestion of administering to a surgical patient a composition comprising a green tea extract and b) at least one NO donor which is a substrate of No synthetase, or a precursor of this NO donor, less than twelve hours, less than six hours or less than three hours before a surgical procedure, as claimed in new claims 30-32. This is not found persuasive and the motivation to do so is discussed below.

Zhong et al. teach that animals are administered green tea extract, begining five days prior to surgery and fasted overnight, as discussed above. Fasted overnight would be mean, to a person of ordinary skill in the art that the animals did not receive any food for about 8-12 hours before the surgery (which was used to administer the green tea extract). Therefore, Zhong et al. was administering the composition up to 12 hours before the surgery. Sherrat teaches that the glutamine is administered 1-2 days before

surgery (see claim 7) and 1-2 days following surgery (see claim 8). Therefore, a person of ordinary skill in the art would reasonably infer that the compound could be administered within a few hours of a surgery. A person of ordinary skill in the art would have a reasonable expectation of success in administering glutamine less than three hours before a surgical procedure because Sherrat discloses an apparent benefit of administration both before and after surgery. Thus it would be reasonable to expect that the benefit is achieved because this compound is in a patient's system during and after the surgery. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success in avoiding ischemia reperfusion injury by administering glutamine at a time close to the time of surgery so that it is in a patient's system at the time of surgery and so it will remain after the surgery, such as less than three hours before a surgery. A person of ordinary skill in the art would have a reasonable expectation of success in administering glutamine with the other compounds instantly claimed in this manner because, as discussed above, they are all known to be either antioxidants or useful specifically in protecting patients from ischemia reperfusion injury which may occur following a surgery.

Applicants also argue that based upon the disclosure of cited references that a skilled person would most likely select a starting time for administration of the composition near the five days prior to surgery disclosed in Zhong et al. to have a better chance of obtaining a reduction in ischemia reperfusion injury from a composition comprising green tea extract and glutamine or green tea extract, glutamine and glycine. Applicants argue that there was no reasonable expectation of success in adjusting the

time of such a composition to a period of time less than 24 hours prior to a surgical procedure and that the time periods cited in the prior art are longer than the period recited in the claims and that there is no disclosure or suggestion in any of the cited references that a time period less than twenty four hours prior to surgery would be effective. This is not found persuasive. As discussed above, Zhong et al. teaches administration which begins several days before surgery and that rats are fasted overnight. Overnight reasonably reads on less than 12 hours or even less than 8 hours, which is less than 24 hours, as instantly claimed.

Applicants also argue that the timing of the administration is not merely a matter of routine optimization and that all of the cited references teach administration at least a day and more than a day prior to surgery. Applicants also argue that for patients in need of emergency surgery, this would not be sufficient. This is not found persuasive, as the references are teaching when the administration begins. Therefore, because the references do not teach particular times which the administration is stopped before surgery, a person of ordinary skill in the art would reasonably understand that the time which the administration is stopped prior to administration could be adjusted according to the circumstances of the surgery.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

## ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELENIE MCCORMICK whose telephone number is (571)272-8037. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MM

/Christopher R. Tate/
Primary Examiner, Art Unit 1655